PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 13 October 2000 (13.10.00)	
International application No. PCT/US00/06364	**Applicant's or agent's file reference** 15280-3771PC
International filing date (day/month/year) 10 March 2000 (10.03.00)	**Priority date** (day/month/year) 12 March 1999 (12.03.99)
Applicant BRENNEMAN, Douglas, E. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 September 2000 (18.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia TEFY

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
15280-3771PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/06364	10/03/2000	12/03/1999
International Patent Classification (IPC) or national classification and IPC A61K38/18		
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/09/2000	01.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Didelon, F Telephone No. +49 89 2399 7332

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/06364

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-50 as originally filed

Claims, No.:

1-33 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

Sequence listing part of the description, pages:

1-8, filed with the letter of 29.06.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-27 (with respect to industrial applicability).

because:

   ☒ the said international application, or the said claims Nos. 1-27 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	28-33
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Comments on item III:

Claims 1-27 relate to methods of treatment of the human/animal body which is subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Comments on item V:

1. Reference is made to the following documents:

   D1: WO 96 11948 A (UNITED STATES DEPT. OF HEALTH AND HUMAN SERVICES, USA) 25 April 1996 (1996-04-25) cited in the application

   D2: WO 98 35042 A (UNITED STATES DEPT. OF HEALTH AND HUMAN SERVICES, USA) 13 August 1998 (1998-08-13) cited in the application

2. The subject-matter of the present application is regarded as novel (Article 33(2) PCT).
   The prior art is silent on the use of ADNF polypeptides I and III or a mixture thereof in the treatment of fetal alcohol syndrome (FAS). Document D2 discloses only that ADNF-III and fragments thereof can be used for the treatment of "pathologies associated with developmental retardation and learning impairments" as well as "pathologies arising with aging and chronic alcohol or drug abuse". However, no specific reference the FAS is made.
   Claims 1-21 are thus novel.

   Pharmaceutical compositions comprising a mixture of ADNF-I and ADNF-III or fragments thereof and their uses in the treatment neurological disorders are not mentioned nor contemplated in D1 or D2.
   Claims 22-27 and 28-33 are thus novel as well.

3. The present application however would not meet the requirements of Article 33(3) PCT because the subject-matter of claims 1-33 is not regarded as inventive:
3.1 Claims 1-21 covers the use of an ADNF polypeptide in the treatment of FAS. In particular it is claimed that (i) an ADNF-I polypeptide like SAL or (ii) an ANDF-III polypeptide like NAP or (iii) a mixture of the two are able to treat fetal alcohol syndrome. It appears however that the experimental data shown do not allow to reach such conclusions.

3.1.1 The results of the water maize test in figure 1 do not show any data concerning the individual use of any of the two ADNF peptides envisaged.
In addition, fig. 2, 3A and 3B do not show nay improvement in the parameters measured, on the contrary, fetal demise seems to be higher with SAL+ alcohol than with alcohol alone (fig. 2). Fetal weight as on fig. 3A seems also to be even reduced with SAL+ alcohol and with alcohol alone. The minimal gain of fetal brain weight shown on fig. 3B does not seem to be significant (1 mg difference appears between SAL+ alcohol and alcohol treatment).

3.1.2 Concerning ADNF-III polypeptides and in particular NAP, an improvement on fetal demise is clear but the other parameters are not convincingly different with respect to the alcohol treatment. Again, figure 1 does not provide any result with NAP alone, and therefore a consistent positive effect to treat FAS cannot be acknowledged.

3.1.3 The mixture of both NAP and SAL (also covered by claims 28-33) appears to have a significant effect on all parameters chosen, but a synergistic effect cannot however be identified because:
- the most relevant test to evaluate the neural function, i.e the water maize does not provide controls with NAP + alcohol nor SAL + alcohol.
- Fig 2 and 3A and B show a quite important standard deviation in the results (see the error bars) which themselves do not sufficiently differ to be able to distinguish between an additive and a synergistic effect.

It results form the above points that the claims 1-21 as well as 28-33 do not solve the technical problem posed, i.e., to provide a treatment of FAS, they appear therefore as non inventive.

3.2 Claims 22-27 , in relation with claims 28-33 are directed to the use of a mixture of ADNF-I and-III polypeptides or fragments thereof for treating neurological disorders associated with neuronal cell death cannot be considered as inventive since no synergistic effect is mentioned in the application. As a consequence it appears to be a mere addition of two compounds individually known from D1 and D2 respectively, without any unexpected effect. In addition the effect of said mixture is not shown for the treatment of FAS, the extrapolation to reduce neuronal cell death in the context of neurological diseases in general therefore is not reasonably acceptable; it is thus considered that the mixture of ADNF-I and -III or fragments thereof do not solve the technical problem posed.
Hence, no inventive can be identified for the subject-matter of claims 22-27 and 28-33.

3.3 In order to allow the Examiner to reconsider whether an inventive step , linked to the presence of a synergistic effect, takes place, the Applicant should provide convincing experimental evidence.

4. For the assessment of the present claims 1-27 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Comments on item IV:

The present application does not satisfy the requirements of unity of invention as defined in Rule 13 PCT.

For an application to be unitary, a novel and inventive common link has to be present.

Since the subject-matter of the present application is not considered as inventive according to the reasons exposed in paragraph 3 of item V, no common link can therefore be identified between the different aspects of the application, which is therefore non-unitary.

Consequently, four distinguished groups of inventions can be identified :

Group 1: Claims 1-3 (partially), 4-7, 16-21 (partially):
The use of an ADNF-I polypeptide or fragments thereof for the treatment of FAS.

Group 2: Claims 1-3 (partially), 8-11, 16-21 (partially):
The use of an ADNF-III polypeptide or fragments thereof for the treatment of FAS.

Group 3: Claims 1-3 (partially), 12-15, 16-21 (partially) and 28-33 (partially):
The use of a mixture of an ADNF-I and ADNF-III polypeptide or fragments thereof for the treatment of FAS.

Group 4: Claims 22-27 and 28-33 (partially):
The use of a mixture of ADNF-I and ADNF-III polypeptides or fragments thereof for the treatment of neurological diseases.

Comments on item VIII:

1. Claims 1 and 22 do not appear to be clear in the sense of Article 6 PCT:

1.1 Claim 1 defines "the reduction of a condition" associated with FAS. This is not considered as quite clear, since it leaves a doubt whether the syndrome is cured or not. The treatment of FAS as such would represent a more appropriate definition.

1.2 Claims 1 and 22 define the protection sought as a result to be achieved, because of the wording "in an amount sufficient to reduce ..." which simply repeats the technical problem (see Guidelines, Ch. III, 4.7).

1.3 The wording "an ADNF polypeptide" , i.e., a single ADNF polypeptide, used in claim 1, is inconsistent with the content of claim 2 which, among other two alternatives, contemplates the use of two peptides together. This latter possibility is absent in the present wording of claim 1.

1.4 Claim 22 is not clear because the wording "for reducing neuronal cell death" does not properly define the subject-matter to be protected, because it is not known which diseases it encompasses.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 September 2000 (14.09.2000)

PCT

(10) International Publication Number
WO 00/53217 A3

(51) International Patent Classification[7]: A61K 38/18, 31/7088, A61P 25/32, 25/28

(21) International Application Number: PCT/US00/06364

(22) International Filing Date: 10 March 2000 (10.03.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/267,511 12 March 1999 (12.03.1999) US

(71) Applicants *(for all designated States except US)*: **THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as represented by THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; Bethesda, MD 20852 (US). **RAMOT OF TEL AVIV UNIVERSITY** [IL/IL]; Tel Aviv University, 69978 Tel Aviv (IL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BRENNEMAN, Douglas, E.** [US/US]; 10601 Santa Anita Terrace, Damascus, MD 20872 (US). **SPONG, Catherine, Y.** [US/US]; 3730 North 25th Street, Arlington, VA 22207 (US). **GOZES, Illana** [IL/IL]; Hamal Street 14, Ramat Hasharon (IL). **BASSAN, Merav** [IL/IL]; Ziporen Street 15A, Givat Poleg, Natania, Hod Hasharon (IL). **ZAMOSTIANO, Rachel** [IL/IL]; Yeshuron Street 17, Hod Hasharon (IL).

(74) Agents: **CHOI, Kathleen** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, 8th floor, San Francisco, CA 94111 (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report:
11 January 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/53217 A3

(54) Title: PREVENTION OF FETAL ALCOHOL SYNDROME AND NEURONAL CELL DEATH WITH ADNF POLYPEPTIDES

(57) Abstract: The invention relates to methods for reducing a condition associated with fetal alcohol syndrome in a subject who is exposed to alcohol *in utero* with an ADNF polypeptide (*e.g*, ADNF I polypeptides, ADNF III polypeptides, or mixtures of ADNF I and ADNF III polypeptides). In one embodiment, the present invention relates to methods for reducing a condition associated with fetal alcohol syndrome in a subject who is exposed to alcohol *in utero* with a mixture of ADNF I and ADNF III polypeptides. The present invention further relates to methods for reducing neuronal cell death by contacting neuronal cells with a mixture of ADNF I and ADNF III polypeptides. Still further, the present invention relates to a pharmaceutical composition comprising a mixture of ADNF I and ADNF III polypeptides.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/06364

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/18 A61K31/7088 A61P25/32 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, CHEM ABS Data, MEDLINE, WPI Data, EPO-Internal, STRAND, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 35042 A (UNITED STATES DEPT. OF HEALTH AND HUMAN SERVICES, USA) 13 August 1998 (1998-08-13) cited in the application abstract page 1, line 1 -page 8, line 20; claims 30-38 ---	22-27
X	WO 96 11948 A (UNITED STATES DEPT. OF HEALTH AND HUMAN SERVICES, USA) 25 April 1996 (1996-04-25) cited in the application abstract page 1, line 1 -page 4, line 16 page 12, line 14 -page 17, line 16; claims 11-13 --- -/--	22-27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2000	18/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Niemann, F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OBERDOERSTER, J. ET AL: "The effects of ethanol on neuronal cell death: Implications for the fetal alcohol syndrome." FASEB JOURNAL, (MARCH 17, 1998) VOL. 12, NO. 4, PP. A134. MEETING INFO.: ANNUAL MEETING OF THE PROFESSIONAL RESEARCH SCIENTISTS ON EXPERIMENTAL BIOLOGY 98, PART 1 SAN FRANCISCO, CALIFORNIA, USA APRIL 18-22, 1998 FEDERATION OF AMERICAN SOCIETIES FOR E, XP002148903 the whole document	1
P,X	SPONG C Y ET AL: "Prevention of fetal alcohol syndrome by novel peptides." FASEB JOURNAL, vol. 13, no. 5 PART 2, 15 March 1999 (1999-03-15), page A881 XP002148904 Annual Meeting of the Professional Research Scientists on Experimental Biology 99;Washington, D.C., USA; April 17-21, 1999 ISSN: 0892-6638 the whole document	1-21, 28-33
P,X	SPINNEY L: "New peptides prevent brain damage 'news!." MOLECULAR MEDICINE TODAY, (1999 JUL) 5 (7) 282. , XP000946706 the whole document	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/06364

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9835042 A	13-08-1998	AU 6322298 A	26-08-1998
		EP 0966533 A	29-12-1999
WO 9611948 A	25-04-1996	AU 707838 B	22-07-1999
		AU 3764195 A	06-05-1996
		EP 0797590 A	01-10-1997
		JP 10509428 T	14-09-1998

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
15280-3771PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 06364	10/03/2000	12/03/1999
Applicant		
THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/US 00/06364

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/18 A61K31/7088 A61P25/32 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, CHEM ABS Data, MEDLINE, WPI Data, EPO-Internal, STRAND, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 35042 A (UNITED STATES DEPT. OF HEALTH AND HUMAN SERVICES, USA) 13 August 1998 (1998-08-13) cited in the application abstract page 1, line 1 -page 8, line 20; claims 30-38 ---	22-27
X	WO 96 11948 A (UNITED STATES DEPT. OF HEALTH AND HUMAN SERVICES, USA) 25 April 1996 (1996-04-25) cited in the application abstract page 1, line 1 -page 4, line 16 page 12, line 14 -page 17, line 16; claims 11-13 --- -/--	22-27

[X] Further documents are listed in the continuation of box C.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2000	18/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Niemann, F

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/US 00/06364

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	OBERDOERSTER, J. ET AL: "The effects of ethanol on neuronal cell death: Implications for the fetal alcohol syndrome." FASEB JOURNAL, (MARCH 17, 1998) VOL. 12, NO. 4, PP. A134. MEETING INFO.: ANNUAL MEETING OF THE PROFESSIONAL RESEARCH SCIENTISTS ON EXPERIMENTAL BIOLOGY 98, PART 1 SAN FRANCISCO, CALIFORNIA, USA APRIL 18-22, 1998 FEDERATION OF AMERICAN SOCIETIES FOR E, XP002148903 the whole document ---	1
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